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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/661,992	09/14/2000	Friedrich Scheiflinger	237.00	8902

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EXAMINER	
HADDAD, MAHER M	

ART UNIT	PAPER NUMBER
1644	

DATE MAILED: 01/02/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/661,992	SCHEIFLINGER ET AL.	
	Examiner	Art Unit	
	Maher M. Haddad	1644	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *09 October 2003*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-16,18,19,23 and 25-27* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-16,18,19,23 and 25-27* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. §§ 119 and 120

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

13)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application) since a specific reference was included in the first sentence of the specification or in an Application Data Sheet. 37 CFR 1.78.

a) ☐ The translation of the foreign language provisional application has been received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121 since a specific reference was included in the first sentence of the specification or in an Application Data Sheet. 37 CFR 1.78.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) *11/14/03*.
4) ☐ Interview Summary (PTO-413) Paper No(s). _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

1. Claims 1-16, 18-19, 23 and 25-27 are pending.

2. Applicant's election with traverse of Group II, claims 1-2, 4-16, 18-19 and 23 (now claims 1-2 and 4-16, 18-19, 23 and 25-27) drawn to an antibody derivative against factor IX/factor IXa, hybridoma, pharmaceutical compositions thereof and a method of producing the antibody filed on 10/09/03, is acknowledged.

Upon reconsideration the examiner has extended the search to cover the claims 1-4, 8-16, 18-19 and 23 of Group I, drawn to an antibody against factor IX/factor IXa.

Applicant's comments that claim 5 was inadvertently omitted from Group II is unclear because claim 5 is included in Group II.

4. Claims 1-16, 18-19, 23 and 25-27 are under examination as they read on an antibody or antibody derivative against factor IX/factor IXa, hybridoma, pharmaceutical compositions thereof and a method of producing the antibody.

5. Claim 7 is objected to under 37CFR 1.821(d) for failing to recite the SEQ ID NOS. in the claim.

6. Claim 7 is objected to because it recites Tyr-Gly-Asn-Ser-Pro-Lys-Gly-Phe-Ala-Tyr (SEQ ID NO:5) twice.

7. The CDR3 peptide of SEQ ID NO: 106 recited in claim 7, is disclosed to be an antibody having anti-FIX or FIXa activity. However, the art recognizes the sequence in claimed SEQ ID NO: 106 as a fragment corresponding to amino acids 697-712 of mature human factor VIII protein. Clarification is required.

8. Claim 16 is objected to under 37 CFR § 1.75(c) as being in improper form because a claim cannot depend on two sets of claims drawn to different features.

9. The following is a quotation of the second paragraph of 35 U.S.C. 112.

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

10. Claims 3, 5-7, 14-16, 23 and 25-27 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

A. The "antibody" recited in claim 3 has no antecedent basis in base claims 1. Base claim 1 only recites an antibody or antibody derivative. Further, the recitation "any one of claim 1" is improper. It is suggested that the permeable be change to " an antibody or antibody derivative according to claim 1, wherein said antibody...".

B. The "antibody derivative" recited in claim 5 has no antecedent basis in base claim 1. Base claim 1 only recites an antibody or antibody derivative. It is suggested that the permeable of claim 5 be change to " an antibody or antibody derivative according to claim 1, wherein said antibody derivative ...". Similarly, the "antibody derivative" in claims 6 and 7 has no antecedent basis in base claims 1, 5 and 6. Further, the "antibody derivative" in claims 25-27 has no antecedent basis in base claim 4.

C. The word "expressing/expressed" in claims 14 and 16, is indefinite because expressed does not indicate the release of the antibodies from the hybridoma. It is suggested that the word "secreted" or "produced" to be used.

D. The "hybridoma clones" and the "hybridoma cell" recited in claim 23 are used in interchangeable. Consistency is required. It is suggested that the "hybridoma clones" be change to hybridoma cells

11. The following is a quotation of the first paragraph of 35 U.S.C. 112:
The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

12. Claim 15 is rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

It is apparent that the hybridoma that produce the 99090924-99090926 and 99121614-99121620 antibodies are required to practice the claimed invention. As a required element, it must be known and readily available to the public or obtainable by a repeatable method set forth in the specification. If it is not so obtainable or available, the enablement requirements of 35 USC 112, a deposit of the hybridoma, which produces this antibody, may satisfy first paragraph. See 37 CFR 1.801-1.809.

If the deposits have been made under the terms of the Budapest Treaty, an affidavit or declaration by applicants or someone associated with the patent owner who is in a position to make such assurances, or a statement by an attorney of record over his or her signature, stating that the hybridoma have been deposited under the Budapest Treaty and that the hybridoma will be irrevocably and without restriction or condition released to the public upon the issuance of a patent would satisfy the deposit requirement made herein. See 37 CFR 1.808. Further, the record

must be clear that the deposit will be maintained in a public depository for a period of 30 years after the date of deposit or 5 years after the last request for a sample *or for the enforceable life of the patent whichever is longer*. See 37 CFR 1.806. If the deposits have not been made under the Budapest treaty, then an affidavit or declaration by applicants or someone associated with the patent owner who is in a position to make such assurances, or a statement by an attorney of record over his or her signature must be made, stating that the deposit has been made at an acceptable depository and that the criteria set forth in 37 CFR 1.801-1.809, have been met.

12. Claims 1-14, and 16, 18-19, 23 and 27 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for an antibody or an antibody derivative against factor IX/factor IXa which increases the procoagulant activity of FIXa in the presence of FVIII inhibitors, wherein the variable region of said antibody derivative comprises amino acids 1-119 and amino acids 135-242 of SEQ ID NO:82, amino acids 1-121 and amino acids 137-249 of SEQ ID NO: 84 or amino acids 1-122 and amino acids 138-249 of SEQ ID NO: 86, does not reasonably provide enablement for any antibody derivative against factor IX/factor IXa which increases the procoagulant activity of FIXa in claim 1 wherein said antibody derivative increases the procoagulant activity of FIXa in the presence of FVIII inhibitors in claims 2, wherein said 3antibody derivative is chimeric antibodies, humanized antibodies, single chain antibodies, bispecific antibodies, diabodies and di-, oligo- or multimers thereof in claim 4 wherein said antibody derivative comprises any complement determining region (CDR) peptide in claim 5, wherein said CDR peptide is a CDR3 peptide in claim 6, wherein said CDR3 peptide comprises an amino acid sequence of SEQ ID NOs: 5, 105, 6, or 106 in claim 7, wherein the variable region of said antibody derivative comprises amino acids 1-119/1-121/1-122 or amino acids 135-244, 137-249/ 138-249 of SEQ ID NOs: 82, 84 or 86, in claims 8, 10 and 12, a pharmaceutical preparation comprising an antibody derivative and a pharmaceutically acceptable carrier in claim 18, the preparation additionally comprising factor IXaα and/or factor IXaβ in claim 19, a method of obtaining an antibody or antibody derivative which interacts with factor IX/factor IXa and increases the procoagulatnt activity of Factor IXa, comprising the steps of immunizing an immunocompetenet mouse with an antigen selected from group consisting of FIX, FIXaα, FIXaβ or **fragments thereof** in claim 23. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

The specification disclosure is insufficient to enable one skilled in the art to practice the invention as broadly claimed without an undue amount of experimentation. Besides the antibodies derivatives having SEQ ID NOs: 82, 84 and 86 and the hybridoma that produce the 99090924-99090926 and 99121614-99121620 antibodies, the specification fails to provide guidance as to how to determine the rest of the CDRs which would encompass any CDRs except the CDR3 recited in claim 7. Further the antibody derivative is made against any fragments of FIX, FIXaα or FIXaβ, the specification fails to provide such fragments.

It is well established in the art that the formation of an intact antigen-binding site generally requires the association of the complete heavy and light chain variable regions of a given

antibody, each of which consists of three CDRs which provide the majority of the contact residues for the binding of the antibody to its target epitope. The amino acid sequences and conformations of each of the heavy and light chain CDRs are critical in maintaining the antigen binding specificity and affinity which is characteristic of the parent immunoglobulin. It is expected that all of the heavy and light chain CDRs in their proper order and in the context of framework sequences which maintain their required conformation, are required in order to produce a protein having antigen-binding function and that proper association of heavy and light chain variable regions is required in order to form functional antigen binding sites. Even minor changes in the amino acid sequences of the heavy and light variable regions, particularly in the CDRs, may dramatically affect antigen-binding function as evidenced by Rudikoff et al (Proc Natl Acad Sci USA 1982 Vol 79 page 1979). Rudikoff et al. teach that the alteration of a single amino acid in the CDR of a phosphocholine-binding myeloma protein resulted in the loss of antigen-binding function. It is unlikely that antibody derivatives as defined by the claims which may contain less than the full complement of CDRs from the heavy and light chain variable regions of a factor IX/factor IXa antibody in unspecified order and fused to any human or nonhuman framework sequence, have the required binding function. The specification provides no direction or guidance regarding how to produce such antibodies derivatives as broadly defined by the claims. Undue experimentation would be required to produce the invention commensurate with the scope of the claims from the written disclosure alone. Further, the specification does not teach that a functional antibody derivative that can be obtained by replacing the CDR3 regions of an antibody with the CDR3 of a donor antibody and still maintain the affinity, specificity in antigen recognition and functionality in increasing the procoagulant activity of FIXa in the presence of FVIII inhibitors. As evidenced by Adair et al. (US Patent 6,632,927) transfer of CDR regions alone are often not sufficient to provide satisfactory binding activity in the CDR-grafted product (col.2 lines 58-61). Panka et al (Proc Natl Acad Sci USA Vol 85 3080-3084 5/88) demonstrate that a single amino acid substitution of serine for alanine results in decreased affinity. Further, Panka et al teaches that the structural change responsible for the binding differences is due to a single amino acid substitution in the H chain framework region at position 94, at the edge of the CDR3. Panka et al teach that the finding that a framework mutation can alter binding to antigen is not unexpected (see Discussion). The scope of the claims must bear a reasonable correlation with the scope of enablement. See In re Fisher, 166 USPQ 19 24 (CCPA 1970).

The CDR3 of SEQ ID NO:105 requires 4 different mutations. It is well known in the art that a single amino acid substitution in CDR3 region correlates with low affinity of an antibody (see Panka et al, supra). Thus it is unpredictable if any functional activity will be shared by two antibodies having less than 100% identity over their CDR3 region.

Despite knowledge in the art for producing monoclonal antibodies to specific sequences, the specification fails to provide guidance regarding which fragments (claim 23) result in variants that retain a similar function. Furthermore, while recombinant techniques are available, it is not routine in the art to screen large numbers of variants where the expectation of retaining similar function is unpredictable based on the instant disclosure.

Also, at issue is whether or not the claimed composition of claims 18-19 would function as pharmaceutical composition. In view of the absence of a specific and detailed description in Applicant's specification of how to effectively use the pharmaceutical composition as claimed, and absence of working examples providing evidence which is reasonably predictive that the claimed pharmaceutical composition are effective for in vivo use, and the lack of predictability in the art at the time the invention was made, an undue amount of experimentation would be required to practice the claimed pharmaceutical composition with a reasonable expectation of success. Further, claim 19 recites the composition further comprising factor IXaα and/or factor IXaβ, however, it is unclear why the antibodies and the antigen are combined in the same composition. Especially, it is known in the art that such combination would neutralize the antibody and/or the antigen.

In view of the quantity of experimentation necessary, the limited working examples, the unpredictability of the art, and lack of sufficient guidance in the specification, it would take undue trials and errors to practice the claimed invention.

13. Claims 1-14, and 16, 18-19 and 23 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

Applicant is in possession of an antibody or an antibody derivative against factor IX/factor IXa which increases the procoagulant activity of FIXa in the presence of FVIII inhibitors, wherein the variable region of said antibody derivative comprises amino acids 1-119 and amino acids 135-242 of SEQ ID NO:82, amino acids 1-121 and amino acids 137-249 of SEQ ID NO: 84 or amino acids 1-122 and amino acids 138-249 of SEQ ID NO: 86.

Applicant is not in possession of any antibody derivative against factor IX/factor IXa which increases the procoagulant activity of FIXa in claim 1 wherein said antibody derivative increases the procoagulant activity of FIXa in the presence of FVIII inhibitors in claims 2, wherein said antibody derivative is chimeric antibodies, humanized antibodies, single chain antibodies, bispecific antibodies, diabodies and di-, oligo- or multimers thereof in claim 4 wherein said antibody derivative comprises any complement determining region (CDR) peptide in claim 5, wherein said CDR peptide is a CDR3 peptide in claim 6, wherein said CDR3 peptide comprises an amino acid sequence of SEQ ID NOs: 5, 105, 6, or 106 in claim 7, wherein the variable region of said antibody derivative comprises amino acids 1-119/1-121/1-122 or amino acids 135-244, 137-249/ 138-249 of SEQ ID NOs: 82, 84 or 86, in claims 8, 10 and 12, a pharmaceutical preparation comprising an antibody derivative and a pharmaceutically acceptable carrier in claim 18, the preparation additionally comprising factor IXaα and/or factor IXaβ in claim 19, a method of obtaining an antibody or antibody derivative which interacts with factor IX/factor IXa and increases the procoagulatnt activity of Factor IXa, comprising the steps of immunizing an

immunocompetenet mouse with an antigen selected from group consisting of FIX, FIXaα, FIXaβ or fragments thereof in claim 23.

Applicant has disclosed only scFV antibodies dervative of SEQ ID NOs: 82, 84 and 86 and the hybridoma that produce the 99090924-99090926 and 99121614-99121620 antibodies of claim 15; therefore, the skilled artisan cannot envision all the contemplated antibody derivative sequence possibilities recited in the instant claims. Consequently, conception cannot be achieved until a representative description of the structural and functional properties of the claimed invention has occurred, regardless of the complexity or simplicity of the method. Adequate written description requires more than a mere statement that it is part of the invention. See *Fiers v. Revel*, 25 USPQ2d 1601, 1606 (CAFC1993). The Guidelines for the Examination of Patent Application Under the 35 U.S.C.112, ¶ 1"Written Description" Requirement make clear that the written description requirement for a claimed genus may be satisfied through sufficient description of a representative number of species disclosure of relevant, identifying characteristics, i.e., structure or other physical and or chemical properties, by functional characteristics coupled with a known or disclosed correlation between function and structure, or by a combination of such identifying characteristics, sufficient to show the applicant was in possession of the genus (Federal Register, Vol. 66, No. 4, pages 1099-1111, Friday January 5, 20001, see especially page 1106 3rd column).

Vas-Cath Inc. v. Mahurkar, 19 USPQ2d 1111, makes clear that "applicant must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession of the invention. The invention is, for purposes of the written description inquiry, whatever is now claimed." (See page 1117.) The specification does not "clearly allow persons of ordinary skill in the art to recognize that [he or she] invented what is claimed." (See Vas-Cath at page 1116.). Consequently, Applicant was not in possession of the instant claimed invention. See University of California v. Eli Lilly and Co. 43 USPQ2d 1398.

Applicant is directed to the Fianl Guidelines for the Examination of Patent Applications Under the 35 U.S.C. 112, ¶ 1 "Written Description" Requirement, Federal Register, Vol. 66, No. 4, pages 1099-1111, Friday January 5, 2001.

14. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless --

(e)(2) the invention was described in a patent granted on an application for patent by another filed in the United States before the invention thereof by the applicant for patent, or on an international application by another who has fulfilled the requirements of paragraphs (1), (2), and (4) of section 371(c) of this title before the invention thereof by the applicant for patent.

The changes made to 35 U.S.C. 102(e) by the American Inventors Protection Act of 1999 (AIPA) and the Intellectual Property and High Technology Technical Amendments Act of 2002 do not apply when the reference is a U.S. patent resulting directly or indirectly from an international application filed before November 29, 2000. Therefore, the prior art date of the reference is determined under 35 U.S.C. 102(e) prior to the amendment by the AIPA (pre-AIPA 35 U.S.C. 102(e)).

15. Claims 1-6, 14, 16, 18, 23, 25 and 27 are rejected under 35 U.S.C. 102(e) as being anticipated by 6,391,299.

The `299 patent teaches Factor IX mAb (BC1, BC2, 9E4(2)F4 and 11G4(1)B9), a chimeric Factor IX mAb (chαFIX) and humanized factor IX mAbs (SB 249413, SB 249415, SB 249416, SB 249417, SB257731 and SB 257732), which are directed against coagulation factor IX and/or IXa (see col. 3., line 60 through col. 4, line 15 in particular). The `299 patent further teaches antibodies can comprise replacement of one or more CDRs from the acceptor antibody with CDRs from a donor antibody as claimed in claim 5 (see col., 5, lines 56-59 in particular). The `299 patent teaches that the SB249413 contains the BC2 heavy chain CDRs representing the heavy chain variable region through and including CDR3 (see col., 23 lines 30-43 in particular) as claimed in claim 6. The `299 patent further teaches a pharmaceutical composition comprising the humanized antibodies or chimeric antibody and a pharmaceutically acceptable carrier (col. 3, lines 15-19 in particular). Finally, the `299 patent teaches a method of obtaining an antibody that interacts with factor IX/factor IXa comprising immunizing female Balb/C mice with human factor IX purified, isolating spleen cells of the immunized mouse, producing hybridoma clones, screening the hybridoma cell supernatants for anti-Factor IX antibodies using an ELISA assay (see col. 17-18, under Preparation and Screening of Anti-Factor IX Monoclonal Antibodies in particular). The `299 patent teaches that these antibodies are used in inhibiting thrombosis (blood clot in the blood vessel) (see the entire document). The`299 patent further teaches Fab fragment or F(ab')2 fragment that produced by chain shuffling whereby the Fd heavy chain of the monoclonal antibodies of the invention is expressed in a murine light chain filamentous phage Fab display library (see col.2 lines 50-54 in particular).

While the prior art disclosure is silent as to the "increases the procoagulant activity of FIXa in the presence of FVIII inhibitors" per se; the referenced antibodies are the same as the claimed antibodies. Therefore, the increase of the procoagulant activity of FIXa in the presence of FVIII inhibitors is considered an inherent property of the reference antibody.

Since the office does not have a laboratory to test the reference antibodies, it is applicant's burden to show that the reference antibody does increases the procoagulant activity of FIXa in the presence of FVIII inhibitors as recited in the claims. See In re Best, 195 USPQ 430, 433 (CCPA 1977); In re Marosi, 218 USPQ 289, 292-293 (Fed. Cir. 1983); and In re Fitzgerald et al., 205 USPQ 594 (CCPA 1980).

The reference teachings anticipate the claimed invention.

16. No claim is allowed.

17. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Maher Haddad, whose telephone number is (703) 306-3472. The examiner can normally be reached Monday to Friday from 8:00 to 4:30. A message may be left on the examiner's voice mail service. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Christina Chan can be reached at (703) 308-3973. Any inquiry of a general nature or relating to the status of this application should be directed to the Technology Center 1600 receptionist whose telephone number is (703) 308-0196.

Papers related to this application may be submitted to Technology Center 1600 by facsimile transmission. Papers should be faxed to Technology Center 1600 via the PTO Fax Center located in Crystal Mall 1. The faxing of papers must conform with the notice published in the Official Gazette, 1096 OG 30 (November 15, 1989). The CM1 Fax Center telephone number is (703) 872-9306.

Maher Haddad, Ph.D.
Patent Examiner
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December 29, 2003

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